PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16095

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

12 OCT 2005

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/038227	06.12.2004	12.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07C235/46, C07D211/46, C07D213/82, C07D401/12, C07D401/14, C07D405/12, C07D409/12

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3 For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-12,14-21(all part), 16-20 with respect to industrial applicability

because.

☒ the said international application, or the said claims Nos. 16-20 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-12,14-21(all part) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-12,14-21(all part) are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	16-21
	No:	Claims	1-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-15,21
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/038227

Re Item III.

The present claims relate to an extremely large number of possible compounds and their use, i.a. due to the variable substitution sites of the various possible rings. The current numerous possibilities included in claim 1 cannot be seen as equivalents, homologues or analogues of the tested examples and therefore are not considered to represent a reasonable generalisation of the examples. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT may only be found for a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of the compounds of formulae (Ib) and (Id) on pages 12 and 13, respectively, thereby including the compounds of claim 13 and all specific examples. This opinion exclusively relates to the searched subject-matter, i.e. to the specific compounds of claim 13 and the claimed use thereof.

Moreover, claims 16-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

Relevant prior art is provided by

(A) WO 03082808
(B) JP 2004002367
(C) WO 2004037800
(E) WO 9933806
(F) EP 1072592
(G) WO 0174806
(H) WO 0248122
(I) WO 0146174
(J) WO 03029233

(K) WO 2004026305
(L) WO 2004080968

(B),(C),(K) and (L) are intermediate documents and as such not considered during the international phase. However, it should be noted that (B) and (C) disclose specific compounds which fall within the scope of formulae (Ib) and (Id). Moreover, (K) and (L) might become relevant for the assessment of inventive step if the current application should prove not to be entitled to the claimed priority. The current compounds essentially differ from (K) and (L) on account of current ring "A".

Novelty

The current compounds of formulae (Ib) and (Id) and of claim 13 appear not to meet the requirements of Article 33(2) PCT since (A) discloses a general formula which overlaps with the said formulae and furthermore one of the current specific compounds, i.e. current example 9. Formulae (Ib) and (Id) essentially differ from (E)-(I) on account of the oxy linker and are considered to represent a novel selection of the general formula of (J).

Inventive Step

The problem underlying the present application appears to be the provision of further opioid receptor modulators which are useful for e.g. drug abuse, eating discorders such as obesity, etc.

(E)-(I) all disclose compounds of the desired use, (J) discloses dopamine receptor ligands which are widely useful for the same diseases treated with an opioid receptor and are thus relevant for the assessment of inventive step, too. In this respect it should be noted that although a discovery of a mechanism a chemical entity triggers in the body may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art. It is only the therapeutic effect of a medicament, i.e. treating specific diseases, which is relevant for the assessment of inventive step within the meaning of Article 33(3) PCT.
E.g. (E) might be considered to represent the closest state of the art. The current compounds essentially differ from the compounds of (E) in that they have an oxy linker in the place of the amine linker of (E). However, looking at (F)-(I) the skilled

person would notice that "A" and "B" may be connected by linkers other than "N": "C" (see (G) or (H)), "CH" (see (I)) or no linker at all (see (F)). Taking further into account that (J) discloses the interchangeability of the said linker being NH, CH_2, OCH_2 or oxygen the skilled person would have contemplated the replacement of the known substituted analogues or the direct bond by oxygen in order to arrive at further compounds with the desired activity. An inventive step in the sense of Article 33(3) PCT may therefore only be acknowledged if the current compounds have an unexpected improved effect vis-à-vis the closest state of the art. Such an effect which has to be valid for all claimed compounds appears not to be derivable from the application documents.

Industrial Applicability

For the assessment of the present claims 16-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.